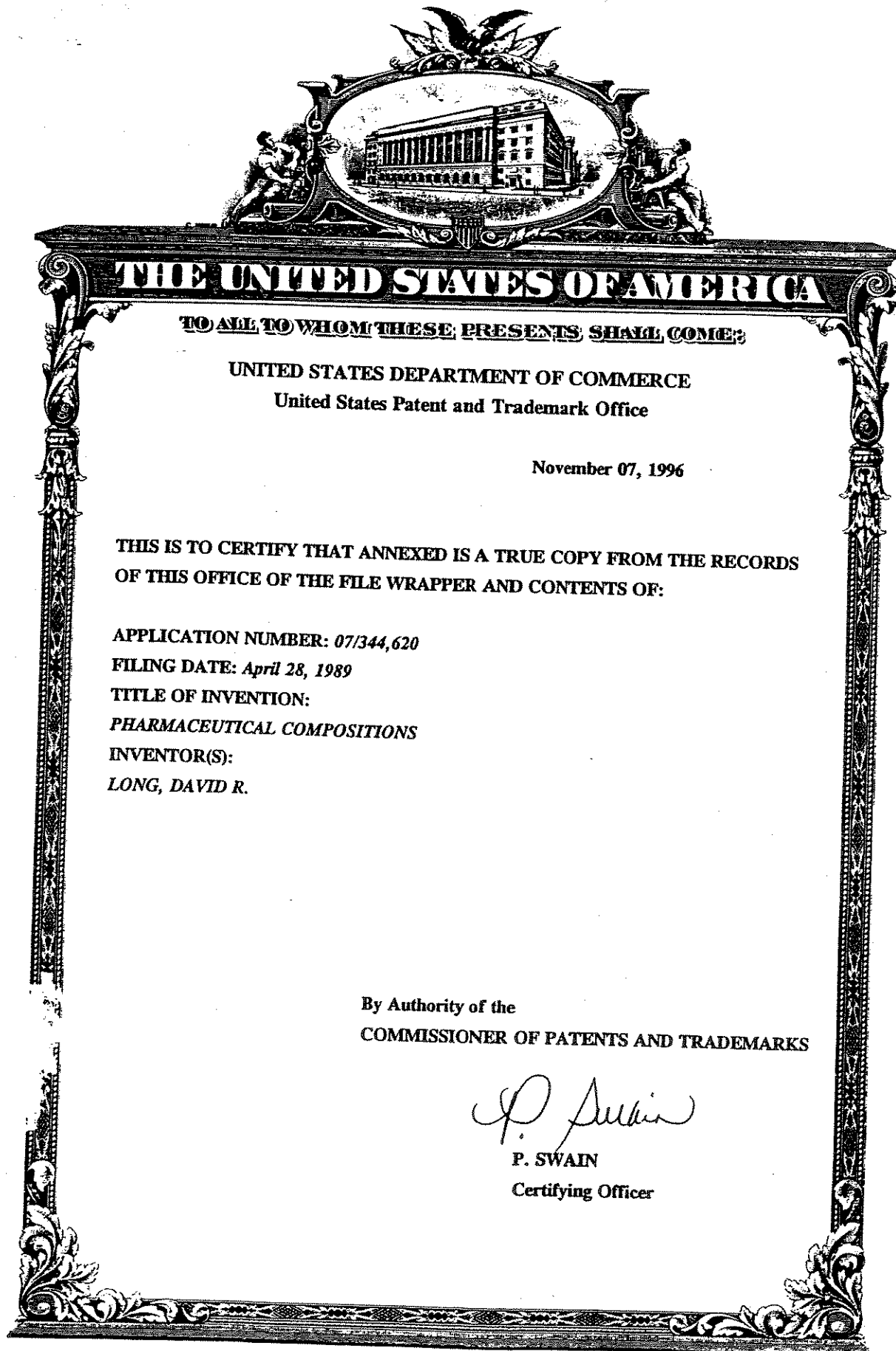


Exhibit 3



G 000111

**G 000112**

**JMBO** (75) **5068249**

**8/234324** **NOV 26 1991** **PATENT NUMBER** **5068249**

<b>SERIAL NUMBER</b> 371494,804	<b>FILING DATE</b> 03/14/93	<b>CLASS</b> 514	<b>MODEL NO.</b> 471 449	<b>GROUP ART UNIT</b> 125	<b>EXAMINER</b> J. J. J. J.
------------------------------------	--------------------------------	---------------------	--------------------------------	------------------------------	--------------------------------

**APPLICANTS**  
DAVID R. LONG, ROYSTON, ENGLAND.

**\*\*CONTINUING DATA\*\*\*\*\***  
 VERIFIED THIS APPLN IS A CON OF 07/344,620 04/28/89 ABN  
 WHICH IS A CON OF 07/131,442 12/11/87 ABN  
Da

**\*\*FOREIGN/PCT APPLICATIONS\*\*\*\*\***  
 VERIFIED UNITED KINGDOM 86 29781 12/12/86  
Da

**GBX**

<b>In priority claimed</b> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	<b>IC 119 conditions met</b> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	<b>AS FILED</b>	<b>STATE OR COUNTRY</b> GB2	<b>SHEETS OR DWS.</b> 0	<b>TOTAL CLAIMS</b> 13	<b>INDEP. CLAIMS</b> 2	<b>FILING FEE RECEIVED</b> \$ 370.00	<b>ATTORNEY'S DOCKET NO.</b>
---	---	-----------------	--------------------------------	----------------------------	---------------------------	---------------------------	---	------------------------------

**Verified and Acknowledged** **Examined** **Entered**

**ADDRESS**  
 RICHARD E. FICHTER  
 BACON & THOMAS  
 625 SLATERS LANE  
 FOURTH FLOOR  
 ALEXANDRIA, VA 22314

**TITLE**  
 PHARMACEUTICAL COMPOSITIONS AQUEOUS RANITIDINE COMPOSITIONS STABILIZED WITH ETHANOL

U.S. DEPT. OF COMMERCE - PAT. & TM. OFFICE - PTO-450L (Rev. 10-78)

G 000113

PATENT APPLICATION SERIAL NO. 07/344620

U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE  
FEE RECORD SHEET

090 05/03/89 344620

1 101 370.00 CK

1556  
(47)

G 000114

PATENT APPLICATION SERIAL NO. 07/494804

U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE  
FEE RECORD SHEET

050	03/22/90	07494804	1 101	370.00 CK
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PTO-1556  
(5/87)

G 000115

U/344620

Locket: REF/H

THE HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

Sir:

☒ This is a request for filing a ☒ continuation ☐ divisional under  
37 CFR 1.60 of pending prior application:

SERIAL NO. 131,442

GROUP ART UNIT: 125

FILED: December 11, 1987

EXAMINER: Friedman

INVENTOR: LONG

TITLE: PHARMACEUTICAL COMPOSITIONS

☒ Enclosed is a copy of the latest inventor signed prior complete application as filed including the specification (including claims), drawings, oath or declaration showing the signature or indication it was signed, and any amendments referred to in the oath or declaration filed to complete the prior application. I hereby verify that the attached papers are a true copy of the latest inventor signed complete prior application Serial No. 131,442 filed on 12-11-87, and that no amendments referred to in the oath or declaration filed to complete the prior application introduced new matter therein, and further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

☐ Cancel in this application original claims \_\_\_\_\_ of the prior application before calculating the filing fee.

☐ A separate Preliminary Amendment is enclosed.

☐ A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 has been filed in prior application Serial No. \_\_\_\_\_ filed \_\_\_\_\_; is enclosed.

☒ The filing fee is calculated as shown below:

ITEM AS FILED *	NO. EXTRA	SMALL ENTITY	FULL FEE
Basic Fee		\$ 185	\$370
Total Claims 14 - 20 =	0	x \$ 0 =	x \$ 12 =
Indep. Claims 2 - 3 =	0	x \$ 18 =	x \$ 36 =
<input type="checkbox"/> Multiple Dep. Cl. in Proper Form Presented, (\$60)			(\$120)
TOTAL			\$ 370

\*Note: All calculations are based on condition of claims after any Preliminary Amendment made pursuant to this communication.

⊖ If less than 20 filed, enter "0". ⊖ If less than 3 filed, enter "0".

☒ A check in the amount of \$ 370 to cover the filing fee is enclosed.

G 000116

494804 -  
07/344620

- 1 -

PHARMACEUTICAL COMPOSITIONS

The present invention relates to a pharmaceutical composition containing as active ingredient the histamine H<sub>2</sub> antagonist ranitidine.

7 Ranitidine, [N-[2-[[[5-(dimethylamino)methyl-2-furanyl]methyl]-thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, and its physiologically acceptable salts are described in British Patent Specification No. 1565966. In that specification there is reference to liquid formulations for oral and parenteral administrations and there is a description of an aqueous based formulation for intravenous use and another of an oral syrup. Both of these formulations contained sufficient hydrochloric acid to achieve a pH of 5.0 and the syrups also contained Sorbitol solution BPC and a flavour as required.

British Patent Application No. GB 2142820A describes aqueous based formulations containing ranitidine and/or one or more of its physiologically acceptable salts thereof having a pH within the range 6.5-7.5. In that specification there is reference to liquid formulations for oral and parenteral administration and there are examples of aqueous formulations for intravenous and oral use. These formulations contain ranitidine hydrochloride and are buffered to a pH of approximately 7 and for intravenous administration the formulations also contain phenol or sodium chloride. For oral administration the formulation also contains hydroxypropylmethyl cellulose as a viscosity enhancing agent, a preservative (parabens), a sweetening agent and a flavour. These compositions have a significantly greater shelf-life over those in British Patent No. 1565966.

We have now surprisingly found that the stability of ranitidine in aqueous based formulations and more particularly aqueous based formulations for oral administration may be substantially enhanced by the addition of ethanol to the formulation.

Thus the present invention provides a pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salts thereof also containing ethanol. The aqueous formulation is prepared using ingredients of a purity such that it is suitable for administration to patients and will in general

G 000117

- 2 -

contain at least one conventional pharmaceutical excipient in addition to the ethanol and ranitidine and/or physiologically acceptable salts thereof.

5 The amount of ethanol present in the formulation is such that the resulting formulation has the enhanced stability. Preferably the amount of ethanol in the composition on a weight/volume-basis of the complete formulation, is within the range 2.5% to 10%, and more particularly is between 5 to 10% w/v, more especially 7-8% w/v.

10 Preferred compositions according to the invention are those in which the pH of the aqueous formulation is within the range 6.5 to 7.5, particularly 6.8 to 7.4 and more especially 7 to 7.3. The required pH of the formulation is preferably obtained by the use of suitable buffer salts for example, potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate or citric acid and disodium  
15 hydrogen orthophosphate.

A preferred embodiment of the invention is an aqueous formulation for oral administration. Such a formulation may comprise ranitidine and/or one or more of its physiologically acceptable salts dissolved in water, ethanol, a preservative and a viscosity enhancing agent. Preferably the required pH of the formulation is obtained by the use of appropriate buffer salts. Optionally the composition may also contain other conventional excipients such as a sweetener, a  
20 flavour and/or flavouring aids.

Examples of suitable preservatives include one or more alkyl hydroxybenzoates such as methyl, ethyl, propyl and/or butyl hydroxybenzoates.

25 Examples of suitable viscosity enhancing agents include Xanthan gum, sorbitol glycerol, sucrose or a cellulose derivative such as carboxymethylcellulose or a salt thereof of a C<sub>1-4</sub> alkyl and/or a hydroxy-C<sub>2-4</sub>alkyl ether of cellulose such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose and hydroxypropylmethylcellulose.

Examples of suitable sweeteners include saccharin sodium, sodium cyclamate, sorbitol and sucrose.

35 Examples of suitable flavouring agents include 'mint' flavours such as peppermint flavouring agents.

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- 3 -

The concentration of ranitidine in the oral formulation, expressed as free base, is conveniently within the range 20-400mg per 10ml, for example 20-200 mg per 10ml, more particularly 150mg per 10ml dose.

5 The amount of ethanol in the formulation for oral administration, expressed as a percentage of the complete formulation on a weight/volume basis, is preferably within the range 2.5 to 10%, and more particularly between 5 to 10%, more especially 7-8%.

10 The amount of viscosity enhancing agent in the formulation will preferably be sufficient to give a solution with a viscosity in the range of 10 to 100 centipoises.

15 The aqueous formulations for oral administration are conveniently prepared by mixing an aqueous solution of ranitidine and/or one or more of its physiologically acceptable salts together with ethanol and the excipients, with aqueous solution or dispersion of the viscosity enhancing agent.

The aqueous formulations according to the invention are preferably prepared using ranitidine in the form of its hydrochloride salt.

20 An illustrative example of a formulation according to the invention is as follows. In this example the relative proportions of ranitidine hydrochloride and the buffer salts are such that the formulation has a pH of approximately 7.

25 Ranitidine oral liquid formulation (150mg/10ml) expressed as free base

	% w/v
30 Ranitidine hydrochloride	1.68
Ethanol	7.5
Potassium dihydrogen orthophosphate	0.095
Disodium hydrogen orthophosphate anhydrous	0.350
Hydroxypropylmethylcellulose	qs
Preservative	qs
35 Sweetening agents	qs
Flavour	qs
Purified water BP to	100ml

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CLAIMS

1. A pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salts thereof, said formulation also containing ethanol.
2. A pharmaceutical composition according to claim 1 containing 2.5% to 10% weight/volume ethanol based on the complete formulation.
3. A pharmaceutical composition according to claim 1 containing 7% to 8% weight/volume ethanol based on the complete formulation.
4. A pharmaceutical composition according to claim 1 having a pH in the range 6.5 to 7.5.
5. A pharmaceutical composition according to claim 1 having a pH in the range 6.8 to 7.4.
6. A pharmaceutical composition according to claim 1 having a pH in the range 7.0 to 7.3.
7. A pharmaceutical composition according to claim 1 wherein said pH is obtained by the use of buffer salts.
8. A pharmaceutical composition as claimed in claim 1 suitable for oral administration.
9. A pharmaceutical composition as claimed in claim 8 containing 20-400 mg ranitidine per 10 ml dose expressed as free base.
10. A pharmaceutical composition according to claim 8 containing 20-200 mg ranitidine per 10 ml dose expressed as free base.

G000120

- 5 -

11. A pharmaceutical composition according to claim 8 containing 150 mg ranitidine per 10 ml dose expressed as 5. free base.

<sup>7</sup>  
~~12.~~ A pharmaceutical composition according to claim 1 prepared using ranitidine in the form of the hydrochloride salt.

10 <sup>11</sup>  
~~13.~~ A pharmaceutical composition which is an aqueous formulation of ranitidine suitable for oral administration containing 150 mg ranitidine per 10 ml dose expressed as free base, said formulation having a 15 pH in the range 7.0 to 7.3 and also containing 7% to 8% weight/volume ethanol based on the complete formulation.

<sup>12</sup>  
~~14.~~ A pharmaceutical composition according to claim <sup>11</sup>~~13~~ wherein said pH is obtained by the use of buffer salts.

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- 6 -

ABSTRACT

- 5      The stability of aqueous formulations of ranitidine or a physiologically acceptable salt thereof is enhanced by the addition of ethanol.

G 000122

Attorney/Docket No. \_\_\_\_\_

DECLARATION FOR PATENT APPLICATION  
AND APPOINTMENT OF ATTORNEY

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention (Design, if applicable) entitled \_\_\_\_\_

Pharmaceutical Compositions

the specification of which (check one): ☐ is attached hereto; ☐ was filed on \_\_\_\_\_ as Application Serial No. \_\_\_\_\_ and was amended on (or amended through) \_\_\_\_\_ (if applicable); was filed as International Application (PCT) No. \_\_\_\_\_ and amended \_\_\_\_\_ (if applicable). I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose information which is material to the examination of this application, in accordance with Title 37, Code of Federal Regulations, §1.56(a). I hereby claim foreign priority benefits under Title 35, United States Code §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

## Prior Foreign Application(s)

86 29781	United Kingdom	12th December, 1986
(Number)	(Country)	(Day/Month/Year Filed)
(Number)	(Country)	(Day/Month/Year Filed)
(Number)	(Country)	(Day/Month/Year Filed)
(Number)	(Country)	(Day/Month/Year Filed)

## Priority Claimed

<input checked="" type="checkbox"/>	<input type="checkbox"/>
Yes	No
<input type="checkbox"/>	<input type="checkbox"/>
Yes	No
<input type="checkbox"/>	<input type="checkbox"/>
Yes	No
<input type="checkbox"/>	<input type="checkbox"/>
Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Appln. SN)	(Filing Date)	(Status - Patented, Pending or Abandoned)
-------------	---------------	---

(Appln. SN)	(Filing Date)	(Status - Patented, Pending or Abandoned)
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I HEREBY DECLARE THAT ALL STATEMENTS MADE HEREIN OF MY OWN KNOWLEDGE ARE TRUE AND THAT ALL STATEMENTS MADE ON INFORMATION AND BELIEF ARE BELIEVED TO BE TRUE; AND FURTHER THAT THESE STATEMENTS WERE MADE WITH THE KNOWLEDGE THAT WILLFUL FALSE STATEMENTS AND THE LIKE SO MADE ARE PUNISHABLE BY FINE OR IMPRISONMENT, OR BOTH, UNDER SECTION 1001 OF TITLE 18 OF THE UNITED STATES CODE AND THAT SUCH WILLFUL FALSE STATEMENTS MAY JEOPARDIZE THE VALIDITY OF THE APPLICATION OR ANY PATENT ISSUED THEREON.

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G 000123

DECLARATION FOR PATENT APPLICATION  
AND APPOINTMENT OF ATTORNEY  
Page 2

Attorney/Docket No. \_\_\_\_\_

OF ATTORNEY: I (We) hereby appoint as my (our) attorneys, with full powers of substitution and to prosecute this application and transact all business in the Patent and Trademark Office connected with this application, J. Ernest Kenney, Reg. No. 19,179; Eugene Mar, Reg. No. 25,893; Richard E. Fichter, Reg. No. 26,382; E. Wolfe, Jr., Reg. No. 28,680; Bruce H. Troxell, Reg. No. 26,592; Thomas J. Moore, Reg. No. 28,974;

and correspondence to: BACON & THOMAS  
625 Slaters Lane - 4th Floor  
Alexandria, VA 22314

Telephone Calls to: \_\_\_\_\_

(703) 683-0500

Full Name of First or Sole Inventor Dr. David Richard Long,		Citizenship British	
RESIDENCE Address - Street 41, Echo Hill,		Post Office Address - Street 41, Echo Hill,	
City Royston,		City Royston	
State or Country Zip Hertfordshire,		State or Country Zip ENGLAND.	
Date 07 Dec. 1987		Signature DR Long	

Full Name of Joint Inventor		Citizenship	
RESIDENCE Address - Street		Post Office Address - Street	
City		City	
State or Country Zip		State or Country Zip	
Date		Signature	

Full Name of Joint Inventor		Citizenship	
RESIDENCE Address - Street		Post Office Address - Street	
City		City	
State or Country Zip		State or Country Zip	
Date		Signature	

Full Name of Joint Inventor		Citizenship	
RESIDENCE Address - Street		Post Office Address - Street	
City		City	
State or Country Zip		State or Country Zip	
Date		Signature	

(See following page(s) for additional joint inventors)

/Continued.....

8

G000124

11/344620 5, 11, 00/10/11

SECRET REF/HA107

THE HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

Sir:

☒ This is a request for filing a ☒ continuation ☐ divisional under  
37 CFR 1.60 of pending prior application:

SERIAL NO. 131,442

GROUP ART UNIT: 125

FILED: December 11, 1987

EXAMINER: Friedman

INVENTOR: LONG

TITLE: PHARMACEUTICAL COMPOSITIONS

☒ Enclosed is a copy of the latest inventor signed prior complete application as filed including the specification (including claims), drawings, oath or declaration showing the signature or indication it was signed, and any amendments referred to in the oath or declaration filed to complete the prior application. I hereby verify that the attached papers are a true copy of the latest inventor signed complete prior application Serial No. 131,442 filed on 12-11-87, and that no amendments referred to in the oath or declaration filed to complete the prior application introduced new matter therein, and further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

☐ Cancel in this application original claims \_\_\_\_\_ of the prior application before calculating the filing fee.

☐ A separate Preliminary Amendment is enclosed.

☐ A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 has been filed in prior application Serial No. \_\_\_\_\_ filed \_\_\_\_\_; is enclosed.

☒ The filing fee is calculated as shown below:

ITEM AS FILED *	NO. EXTRA	SMALL ENTITY	FULL FEE
Basic Fee		\$ 185	\$ 370
Total Claims 14 - 20 = $\textcircled{C}$	0	x \$ 0 =	x \$ 12 =
Indep. Claims 2 - 3 = $\textcircled{C}$	0	x \$ 18 =	x \$ 36 =
<input type="checkbox"/> Multiple Dep. Cl. in Proper Form Presented		(\$60)	(\$120)
TOTAL		\$	\$ 370

\*Note: All calculations are based on condition of claims after any Preliminary Amendment made pursuant to this communication.

$\textcircled{C}$  If less than 20 filed, enter "0".  $\textcircled{C}$  If less than 3 filed, enter "0".

☒ A check in the amount of \$ 370 to cover the filing fee is enclosed.

9

G 000125

- 2 -

☒ The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 CFR 1.16, except claim fees under 1.16(b), (c) or (d) associated with this communication, or credit any overpayment to Deposit Account No. 02-0200. A duplicate copy of this sheet is enclosed.

☐ Informal Drawings are enclosed.

☒ Amend the specification by inserting before the first line the sentence: This application is a ☒ continuation, ☐ division of application Serial No. 131,442, filed December 11, 1987.

G-1

☒ Priority is claimed under 35 USC 119 of application(s):  
 Serial No. 8629781, filed 12-12-86 in U.K.  
 Serial No. \_\_\_\_\_, filed \_\_\_\_\_ in \_\_\_\_\_  
 Serial No. \_\_\_\_\_, filed \_\_\_\_\_ in \_\_\_\_\_  
 Serial No. \_\_\_\_\_, filed \_\_\_\_\_ in \_\_\_\_\_

☒ The certified copy has been filed in prior application  
 Serial No. 131,442 filed 12-11-87

☒ The prior application is assigned of record to

GLAXO GROUP LIMITED

☐ Also enclosed \_\_\_\_\_

☒ The power of attorney appears in the original papers in the prior application, and the power of attorney in the prior application includes: Richard E. Fichter, Registration No. 26,382, of BACON & THOMAS

☒ Address all future communications to:  
 Richard E. Fichter  
 BACON & THOMAS  
 625 Slaters Lane, Fourth Floor  
 Alexandria, Virginia 22314

Respectfully submitted,

*Richard E. Fichter*  
 Richard E. Fichter  
 Reg. No. 26,382 - 01

BACON & THOMAS  
 625 Slaters Lane, Fourth Floor  
 Alexandria, VA 22314  
 (703) 683-0500

Date: April 28, 1989

10

REF/1136

G 000126

FORM PTO-875 REV. 1-88	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO. <b>344620</b>	FILED DATE <b>4-28-89</b>
PATENT APPLICATION FEE DETERMINATION RECORD		APPLICANT (FIRST NAME) <i>Long</i>	

## CLAIMS AS FILED - PART I

FOR:	NO FILED	NO EXTRA
BASIC FEE		
TOTAL CLAIMS		20
INDEP. CLAIMS		3
MULTIPLE DEPENDENT CLAIM PRESENT		

\* If not determined in Col. 1, is more than 20% extra? 0 in Col. 2

## SMALL ENTITY

RATE	FEE
X 6	
X 18	
60	
TOTAL	

OTHER THAN A  
SMALL ENTITY

RATE	FEE
X 12	
X 36	
120	
TOTAL	

## CLAIMS AS AMENDED - PART II

AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NO PREVIOUSLY PAID FOR	PRESENT EXTRA
	13	20	
	2	3	
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM			

## SMALL ENTITY

RATE	ADDIT. FEE
X 6	
X 18	
60	
TOTAL ADDIT. FEE	

OTHER THAN A  
SMALL ENTITY

RATE	ADDIT. FEE
X 12	
X 36	
120	
TOTAL	

AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NO PREVIOUSLY PAID FOR	PRESENT EXTRA
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM			

RATE	ADDIT. FEE
X 6	
X 18	
60	
TOTAL ADDIT. FEE	

RATE	ADDIT. FEE
X 12	
X 36	
120	
TOTAL	

AMENDMENT C	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NO PREVIOUSLY PAID FOR	PRESENT EXTRA
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM			

RATE	ADDIT. FEE
X 6	
X 18	
60	
TOTAL ADDIT. FEE	

RATE	ADDIT. FEE
X 12	
X 36	
120	
TOTAL	

\* If the entry in Col. 1 is less than the entry in Col. 2, enter "0" in Col. 2.  
 \*\* If the highest fee previously paid for in THIS SPACE is less than 20, enter 20.  
 \*\*\* If the highest fee previously paid for in THIS SPACE is less than 3, enter 3.  
 \*\*\*\* If the highest fee previously paid for 1 year or more is the highest number found in the appropriate box in Col. 1.

G 000127

PALM III APPLICATION FILE DATA CODING SHEET U.S. DEPARTMENT OF COMMERCE-PATENT & TM OFFICE

DATE: 5/11/89

FORMAT NO. 2 Serial No. TYPE APPL 07/344620

FILED DATE 07/28/89

GROUP ART UNIT 1235574

CLASS 11

SPECIAL HANDLING 2

SHEETS OF DRAWINGS 11

ASGT? 11

TOTAL CLAIMS 11

INDEPENDENT SMALL CLAIMS 11

SECURITY/FOREIGN CASE? 11

FORMAT NO. 3

ATTORNEY DOCKET NUMBER 11

CONTINUITY CODE 02

FORMAT NO. 4 Applicant's Name & Address

FORMAT NO. 5 Title of Invention

FORMAT NO. 6 & 7 Correspondence

STATUS CODE 2

PARENT FILING DATE 12/1/87

PARENT APPLICATION SERIAL NUMBER 07131442

PARENT PATENT NUMBER

PARENT FILING DATE 12/1/87

PARENT APPLICATION SERIAL NUMBER

PARENT PATENT NUMBER

COUNTRY CODE 43X

PCT/FOREIGN APPLICATION SERIAL NUMBER 8629781

FILING DATE 12/1/86

RECORD 8 0 1

RECORD 8 0 2

RECORD 8 0 3

RECORD 8 0 4

RECORD 8 0 5

RECORD 8 0 6

RECORD 8 0 7

RECORD 8 0 8

RECORD 8 0 9

RECORD 8 1 0

RECORD 9 0 1

RECORD 9 0 2

RECORD 9 0 3

RECORD 9 0 4

RECORD 9 0 5

RECORD 9 0 6

RECORD 9 0 7

RECORD 9 0 8

RECORD 9 0 9

RECORD 9 1 0

FOREIGN PRIORITY CLAIMED? YES NO

APPLICATION PAPERS

MORE ON SUPPLEMENTAL CODING SHEET

MORE ON SUPPLEMENTAL CODING SHEET

MORE ON SUPPLEMENTAL CODING SHEET

G 000128

SER NUMBER 07/344,620	FILING DT 04/28/89	CLASS 514	SUBCLASS RULE 60	ART UNIT 125	EXAMINER
APPLICANTS: DAVID R. LONG, ROYSTON, ENGLAND.					
**CONTINUING DATA** VERIFIED THIS APPLN IS A CON OF 07/131,442 12/11/87					
**FOREIGN/PCT APPLICATIONS** VERIFIED UNITED KINGDOM 8623781 12/12/86					
FORN PRIORITY CLMD YES/NO STATE/ SHEETS TOTAL INDEP. FIL. FEE ATTORNEY'S 35USC119 COND. MET YES/NO COUNTRY DRGS. CLAIMS RECEIVED DOCKET NO. 0 14 2 \$370.00 REF/HA107.					
ADDRESS: RICHARD E. FICHTER BACON & THOMAS 625 SLATERS LANE, FOURTH FLOOR ALEXANDRIA, VA 22314					
TITLE: PHARMACEUTICAL COMPOSITIONS					

13

G000129


**UNITED STATES DEPARTMENT OF COMMERCE**  
**Patent and Trademark Office**

 Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
 Washington, D.C. 20231

 APPLICATION NUMBER: 07/344,620  
 FILING DATE: 04/28/89

LONG

 ATTORNEY DOCKET NO.  
 REF/HAI07

 RICHARD E. FICHTER  
 BACON & THOMAS  
 625 SLATERS LANE, FOURTH FLOOR  
 ALEXANDRIA, VA 22314

 EXAMINER  
 FRIEDMAN, S

 PART UNIT: 125  
 PAPER NUMBER: 3

DATE: 06/28/89

- ☒ This application has been examined ☐ Response to communication filed on \_\_\_\_\_ ☐ This action is made final.

 A shortened statutory period for response to this action is set to expire 3 month(s) 0 days from the date of this letter.  
 Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

- |   |  |
|---|--|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice re Patent Drawing, PTO-846.                   |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1446.                 | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474.     | 6. <input type="checkbox"/> _____  |

**Part II SUMMARY OF ACTION**

1. ☒ Claims 1-4 are pending in the application.  
 Of the above, claims \_\_\_\_\_ are withdrawn from consideration.
2. ☐ Claims \_\_\_\_\_ have been cancelled.
3. ☐ Claims \_\_\_\_\_ are allowed.
4. ☒ Claims 1-4 are rejected.
5. ☐ Claims \_\_\_\_\_ are objected to.
6. ☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on \_\_\_\_\_. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable, ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-846).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on \_\_\_\_\_ has (have) been ☐ approved by the examiner, ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on \_\_\_\_\_, has been ☐ approved, ☐ disapproved (see explanation).
12. ☒ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received.  
☒ been filed in parent application, serial no. 131,442; filed on 12/14/87
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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 EXAMINER'S ACTION

PTOL-326 (Rev. 5-88)

G 000130

Serial No. 07/344,620

-2-

Art Unit 125

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"Also containing ethanol (claim 1) is indefinite as to what else is included. The claims should state how the pH is arrived at.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited in accord with the entire disclosure. See MPEP 706.03(n) and 706.03(z).

All claims should recite amounts for all ingredients.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (1) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same

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Serial No. 07/344,620

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Art Unit 125

person or subject to an obligation of assignment to the same person.

Claims 1-14 are rejected under 35 U.S.C. 103 as being unpatentable over Chem. Absts. all.


The art teaches the cojoined use of use of ranitidine and an alcohol (ethanol). The claims also teach ranitidine and ethanol. The various parameters of the claims; i.e. pH and amounts are <sup>CONSIDERED AS CHOICES TO</sup> one skilled in the art. Such parameters have not been demonstrated as being critical and as such are considered to be within the skill of the art.

All of the claims are rejected over the claims of Serial No. 131,42 on the grounds of double patenting (35 USC 101). No second invention is seen to reside in the instant claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Standley Friedman whose telephone number is (703) 557-9592.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 557-3920.

06/26/89;rbb

  
Stanley J. Friedman  
Primary Examiner  
Group Art Unit 12

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G 000132

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 3-78)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		SERIAL NO. 344,620 194,804		GROUP/ART UNIT 125		ATTACHMENT TO PAPER NUMBER 3	
NOTICE OF REFERENCES CITED				APPLICANT(S) Long					
U.S. PATENT DOCUMENTS									
		DOCUMENT NO.		DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE	
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OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)									
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\* A copy of this reference is not being furnished with this office action.  
(See Manual of Patent Examining Procedure, section 707.05 (a).)

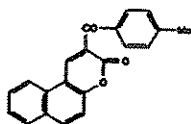
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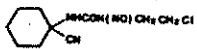
Chemical Abstracts Vol. 97, 1982

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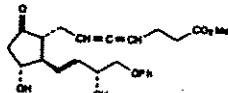


97: 61012a Nitrosourea useful as cytostatic and antitumor agent. Marcel, Richard Fr. Demande FR 2,450,250 (Cl. C07C127/15), 26 Sep 1980, Appl. 79/1,722, 22 Jan 1979; 3 pp.



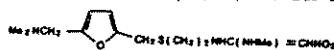
1-(2-Chloroethyl)-3-(1-cyanocyclohexyl)-1-nitrosourea (I) [82498-58-6], m. 81-3°, can be used orally or parenterally or as suppositories as a cytostatic or antitumor agent.

97: 61012f Carbonate diester solutions of PGE-type compounds. Yu, Cheng Der; Bruenner, Ursula (Syntex (U.S.A.), Inc.) U.S. US 4,328,245 (Cl. 424-305; A61K31/215), 04 May 1982, Appl. 234,240, 13 Feb 1981; 6 pp. Prostaglandin E-type



compds. are stabilized by dissolving these compds. in carbonate diester solvents which may contain H<sub>2</sub>O up to the soly. limit of the carbonate diester. Thus, *di-Me 9-keto-11a,15a-dihydroxy-16-phenoxyl-17,18,19,20-tetranorprosta-4,5,13-trans-trienoate* (II) [82444-04-8] at 0.5 mg/mL was dissolved in 0.1% H<sub>2</sub>O-propylene carbonate [108-32-7] and stored at elevated temps. for up to 90 days. The same amt. of the ester was dissolved in propylene carbonate contg. 5% and 10% H<sub>2</sub>O and these solns. stored at 45° for 60 days. The drug was stable in all of these solns.

97: 61014g Crystalline ranitidine hydrochloride and pharmaceutical composition containing it. Crookes, Derek Leslie (Glaxo Group Ltd.) Fr. Demande FR 2,491,067 (Cl. C07D307/52), 02 Apr 1982, GB Appl. 80/31,634, 01 Oct 1980; 16 pp.



Cryst. ranitidine-HCl (I-HCl) [71130-06-8] (form 2) for the treatment of ulcer, allergy, and inflammation cases was prep'd. as has improved filtration and drying properties and reduced hygroscopicity by crystg. I-HCl under controlled conditions in the presence of a hydroxylated solvent, e.g. 2-propanol [67-63-0]. Thus, a mixt. of 20 g I in 5.3 mL HCl, 130 mL 2-propanol, and 4 mL H<sub>2</sub>O was heated at 50° while adding an addnl. 68 mL 2-propanol, then the mixt. cooled to 10-12° and the crystd. product (form 2), m. 139-141°, was sepd. and recrystd. in 2-propanol-H<sub>2</sub>O mixt. (66:9). The IR and x-ray spectra of I-HCl are reported.

97: 61015h Buffers for the stabilization of eye lotions containing chlorobutanol. Lion Corp. Jpn. Kokai Tokkyo Koho JP 82 62,216 (Cl. A61K9/08), 15 Apr 1982, Appl. 80/137,431, 01 Oct 1980; 5 pp. Eye lotions contg. chlorobutanol [57-15-8] are prep'd. with buffering agents such as *ε*-aminocaproic acid [60-32-2], citric acid [77-32-9], NaH<sub>2</sub>PO<sub>4</sub>, Na aspartate [17090-93-6], and Na glutamate [16177-21-2] which prevent the hydrolysis of chlorobutanol during storage. Thus, an eye lotion was prep'd. by combining propylene glycol 0.5, chlorobutanol 0.3, *ε*-aminocaproic acid 0.07, citric acid 0.0653%, NaCl (an amt. required to produce an equitonicity with resp. to tears), and water (balance).

97: 61016j Transparent eye lotions containing glycyrrhizates and cationic surfactants. Lion Corp. Jpn. Kokai Tokkyo Koho JP 82 62,219 (Cl. A61K9/08), 15 Apr 1982, Appl. 80/137,432, 01 Oct 1980; 3 pp. A transparent eye lotion contg. bactericidal cationic surfactants and glycyrrhizinate is obtained by adjusting the pH to 5.9-7.0. Thus, such a soln. was prep'd. by combining *di-K glycyrrhizinate* [68797-35-3] 0.1, benzalkonium chloride 0.1, H<sub>3</sub>PO<sub>4</sub> 1.85, borax 0.032, and water to 100% by wt. The borax concn. produced a pH of 5.9, but less concn. tended to decrease the pH and cause the formation of opacity which decreases the com. value.

97: 61017k Topical solutions producing a cool sensation. Lion Corp. Jpn. Kokai Tokkyo Koho JP 82 62,221 (Cl. A61K9/08), 15 Apr 1982, Appl. 80/138,086, 02 Oct 1980; 4 pp. 1-Menthol [12216-51-5] low molecular alcoh. and nolvaine added to

was ineffective.

97: 61018m Mesocyclic antitumor compositions and methods for using them in the treatment of cancer. Henry, David W.; Ryan, Kenneth J.; Grange, Edward W. U.S. US 4,329,355 (Cl. 424-272; A61K31/42), 11 May 1982, Appl. 16,384, 01 Mar 1979; 5 pp. Antitumor compns. comprise the title compds. I (R<sup>1</sup>



= Ph or substituted Ph; R<sup>2</sup> = H or Me) and their salts. A tablet formulation contained anhydrous 5-(methylamino)-3-phenyl-1,2,3,4-oxatriazolium hydroxide-HCl (II) [82333-27-5] 15, lactose 86, corn starch 45.5, gelatin 2.5, and Mg stearate 1 mg/tablet. II was prep'd. by addn. of HCl to 4-methyl-1-phenyl-3-thiosemicarbazide [13207-60-6], followed by addn. of NaNO<sub>2</sub> to the mixt. The biol. activities of various I were demonstrated against lymphocytic leukemia P388 implanted in mice.

97: 61019a Radiopaque cyanoacrylate compositions. Kraft, Robert E. (Population Research, Inc.) Eur. Pat. Appl. EP 58,457 (Cl. C09J3/14), 28 Apr 1982, US Appl. 198,466, 20 Oct 1980; 19 pp. The title compds., useful in medicinal and industrial application, comprise an alkyl 2-cyanoacrylate monomer and a radiopaque additive such as an org. iodo compd., cyanoacrylate stable inorg. compd., or org. iodo compd. compn. contg. sterile redistd. Me 2-cyanoacrylate [137-46-3], iodoform [75-47-8], 2,4,6-triiodophenol [609-23-4] 1.17 mol % each, 250-750 ppm (mole basis) SO<sub>2</sub> as stabilizer and 250 ppm hydroquinone (to decrease light sensitivity) was heated with stirring at 80° for 1 h in the dark. The resulting compn. contg. 7% I atoms can be stored for extended time periods in Al foil. The compn., if exposed to light just prior to use, is stable for 2-3 h and when used as female sterilizing agent the polymer plug formed in the fallopian tube is distinguishable over the pelvic background and an x-ray image.

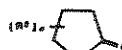
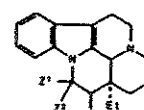
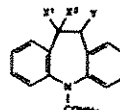
97: 61020f Enhancement of drug absorption from suppositories by saponins. Fujisawa Pharmaceutical Co., Ltd. Jpn. Kokai Tokkyo Koho JP 82 64,610 (Cl. A61K9/02), 19 Apr 1982, Appl. 80/141,345, 08 Oct 1980; 4 pp. Drugs not readily absorbable in the digestive tract are formulated in suppositories in mixts. with saponins, which accelerate absorption from the colon. For example, 100 mg cephalosporin Na, 100 mg saponin, and 2 g Miglyol-812 (fatty acid glyceride) were mixed and molded to give a suppository. Cephalosporin Na was absorbed rapidly from this suppository in rats, and 70% of the dose was excreted in 24 h; without the saponins, only 18% was excreted in 24 h.

97: 61021g Coated acetylsalicylic acid formulation. Dreher, Dieter; Lehmann, Klaus; Boessler, Heide (Roehm G.m.b.H.) Eur. Pat. Appl. EP 50,191 (Cl. A61K9/28), 28 Apr 1982, DE Appl. 3,039,073, 16 Oct 1980; 17 pp. Acetylsalicylic acid (I)



[50-78-2], with a particle size <3mm, is coated in a fluidized bed or a coating pan with an aq. dispersion of a polymer, esp. of an acrylic or methacrylic acid contg. 8-30% CO<sub>2</sub>H groups. The H<sub>2</sub>O of the dispersion is evap'd. to form the film coating, and the product has <0.2% by wt. free salicylic acid. Thus, I crystals (0.3-0.8 mm) contg. 0.01% salicylic acid were coated with 2.5% by wt. of a pH 2.5, 30% aq. dispersion of a copolymer of Et acrylate 62, Me methacrylate 37, and methacrylic acid 1%, contg. 0.4% Na lauryl sulfate and 6% polyoxyethylene sorbitan monooleate as emulsifiers. The inlet and exit air temps. were 40 and 30°, resp. The product contained 0.21% H<sub>2</sub>O and 0.04% salicylic acid. The coatings inhibited hydrolysis in storage.

97: 61022h Pharmaceutical compositions with an antiepileptic and antineuralgic effect. Mondadori, Cesare; Schmutz, Markus (Ciba-Geigy A.-G.) Eur. Pat. Appl. EP 50,583 (Cl. A61K31/55), 28 Apr 1982, CH Appl. 80/7,775, 17 Oct 1980; 23 pp. Pharmaceuticals for treating epilepsy and neuralgia



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I. R-CH<sub>2</sub>(Z)NH<sub>2</sub>  
II. R-CH<sub>2</sub>NH<sub>2</sub>

1-Et; R<sup>2</sup> = Me or iso-Pr; X = O or S; Y = CH<sub>2</sub> or CH<sub>2</sub>S(CH<sub>2</sub>)<sub>2</sub>; Z = O, S, CN, or CHNH<sub>2</sub>; II: R<sup>1</sup> = H or 1- or 3-Et; R<sup>2</sup> = H, Me, CH<sub>2</sub>Ph, 4-chlorobenzyl, or methylenedioxyphenylmethylene; R<sup>3</sup> = H, iso-Pr, cyclopentyl, cyclohexyl, 4-chlorobenzyl, etc.; R<sup>4</sup>R<sup>5</sup> = (CH<sub>2</sub>)<sub>4</sub> with the cyclization of 4-(2-hydroxyethyl)imidazole. [672-82-2] or diethylacetal [645-36-3]. I and II were tested for antitumor activity in a stress-induced ulcer model in rats, H<sub>2</sub>-receptor antagonist in mice. Compds. exhibiting substantial antitumor activity and toxicity in screening dose (5 mg/kg) were evaluated by full dose-range studies. None of the compds. showed anticholinergic, antihistaminic, or significant gastric antisecretory action (tested for only a few compds.). Some structure-activity relations are considered.

104:102274a Effects of verapamil and propranolol on the leukotriene D<sub>4</sub>-induced bronchoconstriction in the isolated and perfused guinea pig lung. Trockle, G.; Catu, G.; Febvre, N.; 54001 Nancy, Fr.). *J. Pharmacol.* 1985, 16(4), 454-8 (Fr.). The bronchoconstriction caused by perfusion of the isolated guinea pig lung with leukotriene D<sub>4</sub> [73836-78-9] (0.2 x 10<sup>-6</sup> M) was the high concn. of verapamil used (20 and 60 mg/L). However, at not related to its Ca<sup>2+</sup>-blocking properties. The constrictor effects of leukotriene were not stimulated by perfusion with propranolol (525-66-6) contrary to previous results in vivo.

104:102275b Cimetidine inhibition of dimaprit-induced writhing in the rat. Scarpinato, Carmelo; Del Soldato, Piero (Inst. 1985, 32(4), 237-40 (Eng). Dimaprit (l.p.)-induced writhing, a pentadently blocked by cimetidine (I) [51481-61-9] was dose-dep. (mg/kg) administered orally 1 h prior to dimaprit. No writhing was observed in rats injected i.v. with dimaprit, indicating that the H<sub>2</sub>-receptor agonist acts at peripheral nociceptive terminals within the peritoneum. These results are discussed in terms of the specific H<sub>2</sub>-receptor-related analgesic effect of I in relieving epigastric pain of duodenal ulcer patients.

104:102276c Effect of cimetidine on immune response. Aoi, K.; Hosokawa, Tomohide; Kawai, Keiichi (Dep. Prev. Med., Kyoto Prefect. Univ. Med., Kyoto, Japan 602). *Agaku no Ayumi* 1985, 135(11), 993-4 (Japan). The effect of cimetidine [51481-61-9] on immune response was studied in vitro. The no. of anti-SRBC-PFC cimetidine. The anti-DNP-ficol antibody response did not change with 10<sup>-3</sup>-10<sup>-4</sup> M of cimetidine. It appears that cimetidine increases the immune response by modulating T-cell responses.

104:102277d The effect of verapamil is reduced in isolated airway smooth muscle preparations lacking the epithelium. Rabin, David; Hay, Douglas W. P.; Robinson, Victor A.; Farmer, Stephen G.; Fleming, William W.; Fedan, Jeffrey S. (Div. Respir. Dis. Stud., Natl. Inst. Occup. Saf. Health, Morgantown, WV 26505 USA). *Life Sci.* 1986, 38(9), 809-16 (Eng). The effect of epithelium removal on the reactivity of rabbit airway smooth muscle was studied in vitro, using preps. from several levels within the respiratory tree, i.e., trachea, primary (1°) and secondary (2°) bronchus. Methacholine [55-92-3] contracted tissues from all 3 levels of the airway. Histamine [51-45-6] contracted strips from 2° bronchus, had an inconsistent action in strips from 1° bronchus and no without effect in tracheal preps. K<sup>+</sup> contracted tissues from the trachea and 1° bronchus, and had a mixed action in 2° bronchial strips. Removal of the epithelial cell layer variably affected the reactivity of the smooth muscle to the 3 agents studied. In 2° bronchus, epithelium removal potentiated responses to histamine and methacholine. In 1° bronchus, only responses to methacholine were consistently augmented. In tracheal preps, epithelium removal did not alter the reactivity of the tissue to any agent examd. Verapamil (10<sup>-6</sup> M) attenuated responses to all agents and increased in its potency from tracheal through 1° to 2° bronchial preps. Following epithelium removal, verapamil was substantially less effective in 2° bronchus, yet its effects were unchanged in the trachea. Apparently, the magnitude of the effect of verapamil on airway smooth muscle is, in part, related to the presence of the epithelium.

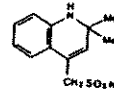
104:102278e Effects of ranitidine and cimetidine on plasma proteins in healthy subjects. Howden, C. W.; Fletcher, C. D.; Smith, E.; Reid, J. L. (Dep. Mater. Med., Stobhill Gen. Hosp., Glasgow, UK G21 3UW). *J. Clin. Pharmacol.* 1986, 26(2), 97-9 (Eng). Serum lipoproteins were monitored in 24 healthy subjects receiving either ranitidine [66357-35-5] or cimetidine [51481-61-9] for 4 wk. Ranitidine produced a significant redn. in high-d. protein (HDL)-cholesterol [57-88-5] in both men and women. Redn. in LDL-cholesterol that was significant only in women. As the drugs had opposite effects on HDL-cholesterol levels, the mechanism of action is unlikely to be mediated by H<sub>2</sub>-receptor blockade.

104:102279f Augmented postprandial gastric acid secretion due to exposure to ranitidine in healthy subjects. Frislid, Karin; Aadland, E.; Berstad, A. (Med. Dep., Lovisenberg Hosp., Oslo, Norway). *Scand. J. Gastroenterol.* 1986, 21(1), 119-22 (Eng). In 10 healthy volunteers gastric acid output in response to a meal was significantly increased 60-64 h after cessation of a 4 wk of ranitidine [66357-35-5] treatment as compared with the response before treatment. Four to 6 wk after discontinuation of treatment the acid secretory response to the meal had returned to values not significantly different from those seen before treatment. There was no change in pepsin [9001-75-6] output owing to ranitidine treatment.

104:102280g Effect of ranitidine on meal-induced gastric acid secretion and the influence of adding ethanol to the meal. Frislid, Karin; Berstad, A. (Med. Dep., Lovisenberg Hosp., Oslo, Norway). *Scand. J. Gastroenterol.* 1986, 21(1), 123-8 (Eng). The effect of ranitidine [66357-35-5] on meal-stimulated pepsin [9001-75-6] and acid secretion 3-4 after administration of the drug was compared in 10 healthy volunteers. The results showed an insignificant redn. of pepsin output, whereas acid output was reduced by 78.5%, demonstrating the difference in response of the chief and parietal cells to an H<sub>2</sub>-receptor antagonist. Adding EtOH [64-17-5] to the meal did not reduce the acid-inhibiting effect of ranitidine.

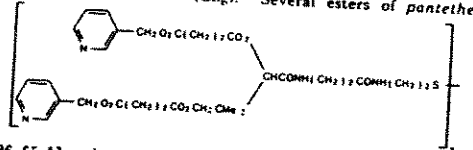
104:102281a Effect of theophylline on membrane potential and contractile force in hamster diaphragm muscle in vitro. Esau, Sharon (Dep. Intern. Med., Univ. Virginia, Charlottesville, VA 22908 USA). *J. Clin. Invest.* 1986, 77(2), 638-40 (Eng). The effect of theophylline [58-55-9] on resting membrane potential and tension in hamster diaphragm cells was studied. Resting membrane potential was 76 mV in Krebs soln. and increased to -85 mV with added theophylline. Tension increased from 5% (at 100 Hz) to 20% (at 10 Hz) with theophylline. Hyperpolarization indicates an increase in intracellular to extracellular K<sup>+</sup> concn. Net K<sup>+</sup> outflow occurred with each contraction, causing the cell membrane to become depolarized with repeated contraction, ultimately leading to fatigue. The hyperpolarization of the skeletal muscle cell membrane obsd. with theophylline may play an important role in prolonging time to fatigue.

104:102282b Effect of a dihydroquinoline-type antioxidant (Ch-402) on lipid peroxidation in brain homogenate and microsomes of the rat and mouse. Anna, Blazovica; Dezso, Ambrus; Aniko, Somogyi; Istvan, Lang; Janos, Feher (Belgyogyszati Klin., Semmelweis Orvostud. Egy. Arterioscl. Kutatócsoport, Budapest, Hung.). *Kiserl. Orvostud.* 1985, 37(5), 488-92 (Hung). The antioxidant CH-402 (I) [75903-70-7] inhibited



ascorbate-induced lipid peroxidn. in brain homogenates and subcellular fractions from brains of rats and mice. The inhibition was concn.-dependent at 10<sup>-4</sup>-10<sup>-2</sup> M. Lipid peroxidn. was detd. by measurement of malondialdehyde [542-78-9] prodn.

104:102283c Pantetheine and pantetheine esters with hypolipidemic nicotinic acid derivatives. Piccinola, G.; Calvi, E.; Ravenna, F.; Gentili, P.; Manzardo, S.; Riva, M. (Dep. Chem. Res., Maggioni Farmaceutici S.p.A., I-20133 Milan, Italy). *Arzneim.-Forsch.* 1983, 35(12), 1766-71 (Eng). Several esters of pantetheine



[496-65-1] and pantetheine [16516-67-4] were prepd., resp., with 3-pyridineacetic acid [501-81-3] and with 3-(3-pyridinemethoxy)carbonylpropionic acid [34663-38-2], and these products were tested for their capacity to lower serum nonesterified fatty acids and triglycerides in normal rats. Among the products tested, MG 28362 (I) [96922-80-4] had marked hypolipidemic activity, the action being of uncommonly long duration.

104:102284d Pharmacological study of a new hypolipidemic drug of prolonged activity, the tetraester of pantetheine with 3-(3-pyridinemethoxycarbonyl)propionic acid. Gentili, P.; Manzardo, S.; Riva, M. (Dep. Pharmacol., Maggioni Farmaceutici S.p.A., I-20133 Milan, Italy). *Arzneim.-Forsch.* 1985, 35(12), 1772-7 (Eng). The hypolipidemic activity of the title compd., MG 28362 (I) [96922-80-4], was assessed under various exptl. conditions and was compared to those of nicotinic alc., nicotinic alc. hemisuccinate, nicotinic acid, and pantetheine tetranicotinate. In the normolipidemic rat, MG 28362 causes a more prolonged redn. of nonesterified fatty acids (NEFA) and serum triglycerides than the ref. products. NEFA values return slowly to pretreatment levels without the rebound effect typical of most nicotinic acid derivs. Likewise in the test of EtOH-induced hypertriglyceridemia, MG 28362 shows more pronounced and sustained activity than the ref. products. It is also more effective against Triton-induced hyperlipidemia and against diet-induced hypercholesterolemia; in the latter test, MG 28362 caused no triglyceride accumulation in the liver. Even at high dosage levels,

G 000135

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application Serial No.: 07/344,620

Applicant: David R. LONG

Group Art Unit: 125

Filing Date: April 28, 1989

Examiner: Friedman

For: PHARMACEUTICAL COMPOSITIONS

PETITION FOR EXTENSION OF TIME

Honorable Commissioner of Patents  
and Trademarks  
Washington, DC 20231

Sir:

Applicant requests that the time for taking action in this case be extended pursuant to 37 CFR 1.136 (a) for:

- ☒ one month      ☐ three months  
☐ two months      ☐ four months

The fee set in 37 CFR 1.17 for the extension of time is  
\$ 62.00.

☒ Fee enclosed. Please charge any additional fee required for this extension of time to Deposit Account No. 02-0200. A duplicate copy of this paper is enclosed.

☐ Charge fee to Deposit Account No. \_\_\_\_\_. A duplicate copy of this paper is enclosed.

☐ Applicant is a small entity entitled to pay reduced fees in this application. A verified small entity statement:

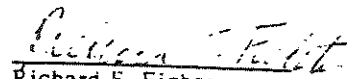
- ☐ has been filed      ☐ is enclosed

Also enclosed is a:

- ☒ Response      ☐ Notice of Appeal      ☐ Appeal Brief

☒ PTO Form 1449 with attached reference cited therein

Respectfully submitted,

  
Richard E. Fichter  
Reg. No. 26,382

BACON & THOMAS  
625 Slaters Lane - Fourth Floor  
Alexandria, Virginia 22314  
(703) 683-0500

Date: October 30, 1989

G 000136

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application Serial No.: 07/344,620

Applicant: David R. LONG

Group Art Unit: 125

Filing Date: April 28, 1989

Examiner: Friedman

For: PHARMACEUTICAL COMPOSITIONS

PETITION FOR EXTENSION OF TIME

Honorable Commissioner of Patents  
and Trademarks  
Washington, DC 20231

Sir:

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☐ Applicant is a small entity entitled to pay reduced fees in this application. A verified small entity statement:

☐ has been filed

☐ is enclosed

Also enclosed is a:

☒ Response

☐ Notice of Appeal

☐ Appeal Brief

☒ PTO Form 1449 with attached reference cited therein

Respectfully submitted,

*Richard E. Fichter*  
Richard E. Fichter  
Reg. No. 26,382

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625 Slaters Lane - Fourth Floor  
Alexandria, Virginia 22314  
(703) 683-0500

Date: October 30, 1989

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115

G 000137

- 2 -

☒ The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 CFR 1.16, except claim fees under 1.16(b), (c) or (d) associated with this communication, or credit any overpayment to Deposit Account No. 02-0300. A duplicate copy of this sheet is enclosed.

☐ Informal Drawings are enclosed.

☒ Amend the specification by inserting before the first line the sentence: This application is a ☒ continuation, ☐ division of application Serial No. 131,442, filed December 11, 1987.

☒ Priority is claimed under 35 USC 119 of application(s):  
 Serial No. 8629781, filed 12-12-86 in U.K.  
 Serial No. \_\_\_\_\_, filed \_\_\_\_\_ in \_\_\_\_\_  
 Serial No. \_\_\_\_\_, filed \_\_\_\_\_ in \_\_\_\_\_  
 Serial No. \_\_\_\_\_, filed \_\_\_\_\_ in \_\_\_\_\_

☒ The certified copy has been filed in prior application  
 Serial No. 131,442 filed 12-11-87

☒ The prior application is assigned of record to

GLAXO GROUP LIMITED

☐ Also enclosed \_\_\_\_\_

☒ The power of attorney appears in the original papers in the prior application, and the power of attorney in the prior application includes: Richard E. Fichter, Registration No. 26,382, of BACON & THOMAS

☒ Address all future communications to:  
 Richard E. Fichter  
 BACON & THOMAS  
 625 Slaters Lane, Fourth Floor  
 Alexandria, Virginia 22314

Respectfully submitted,

*Richard E. Fichter*  
 Richard E. Fichter  
 Reg. No. 26,382

BACON & THOMAS  
 625 Slaters Lane, Fourth Floor  
 Alexandria, VA 22314  
 (703) 683-0500

Date: April 28, 1989

G 000138